Review Article

Neurologic Complications of Infectious Mononucleosis

Kevin P. Connelly, DO* and L. Dana DeWitt, MD†

A review of the neurologic complications of Epstein-Barr viral (EBV) infections is presented. EBV has been associated with a wide range of acute neurologic diseases in children. Encephalitis, meningitis, cranial nerve palsies, mononeuropathies, and many other neurologic ailments have been described since the confirmation of EBV as the etiology of infectious mononucleosis. It is important to recognize that EBV can cause a myriad of neurologic illnesses with or without the stigmata of infectious mononucleosis.

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Introduction

Although nervous system manifestations of infectious mononucleosis (IM) have been reported in the literature for over 60 years [1,2], the Epstein-Barr virus (EBV) is frequently overlooked as a causative agent of neurologic disease in the pediatric population. This is mainly due to the timing or lack of IM manifestations with the neurologic insult. Many reports described purely neurologic presenting symptoms and clinical manifestations of IM [3-6]. In a chart review of 144 IM patients—the majority of whom were pediatric—Silverstein found that the incidence of objective neurologic involvement was 5.5% with a range reported in the literature of 0.37-7.3% [3].

Historic Antecedents

Although it is a familiar disease to today's physicians, the etiology and pathogenicity of IM had not been well understood until the late twentieth century. The term, infectious mononucleosis, was first used in 1920 to describe the clinical picture of medical students attending Johns Hopkins University who had associated atypical mononuclear cells with the illness; however, it was not until 1968 that researchers were able to link EBV with IM [7].

Clinical Course

EBV (a herpes-type DNA virus) is a cause of IM, which is a benign, acute viral illness common in children and young adults. Its usual course is a 7-day prodromal illness, followed by a 4-day to 3-week acute illness of fever, pharyngitis, lymphadenopathy, splenic enlargement (in 50% of patients), and mononuclear leukocytosis with atypical lymphocytes. IM is usually less severe in young children than in older children or young adults. In fact, primary infections are often asymptomatic in children [8-10].

Epidemiology

Transmission occurs mostly by oropharyngeal secretions or respiratory droplets, as viral particles are replicated in oropharyngeal tissues, which accounts for the synonym, "the kissing disease" [8,9]. EBV is highly specific in its host cell, in that only bone-marrow-derived human lymphocytes (B-cells) are infected. Lymphoid tissues, including lymph nodes, spleen, and tonsils, become infiltrated with atypical mononuclear cells [9].

Diagnosis

Neurologic complications are the most frequent cause of death in IM; however, the majority of patients have benign outcomes, with 85% recovering completely. Neurologic signs and symptoms may be the first or only manifestations of the illness [6,11,12]. The etiology of EBV can be overlooked when the classic presenting symptoms are not evident. In many patients, the heterophil antibody is negative, atypical lymphocytes may be low in number or delayed in appearance, and the diagnosis must be made by changes in EBV-specific antibodies [10]. In early acute-phase serum, detection of antiviral capsid antigen (VCA) titers of 1:320 or higher, presence of anti-D (i.e., diffuse component of EBV-induced early antigen complex), or EBV VCA IgM antibodies and the absence of antibodies to virus-associated nuclear antigen (anti-EBNA IgG) denotes a current infection. In subsequent serum specimens, fourfold or greater increments in anti-VCA or anti-D titers, or late declines in anti-VCA titers or loss of

From the Departments of *Pediatric Neurology and †Neurology; New England Medical Center Hospitals; Boston, Massachusetts.

Communications should be addressed to:
Dr. Connelly; Children's Medical Center; Medical College of Virginia; MCV Box 1338; Richmond, VA 23298.
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anti-D titers, and the appearance of antibodies to virus-associated nuclear antigen (anti-EBNA IgG) denotes a recent infection. These criteria are based on the immunologic response to EBV infection. In the early acute phase, anti-VCA titers peak, then decline to persistent lower levels. Anti-D responses and virus-specific IgM antibodies are limited to a few weeks. Late in convalescence, anti-EBNA antibodies occur and persist for life [4].

Neurologic Complications

Because EBV may present atypically and has been associated with a myriad of neurologic diseases, EBV should be considered in all acute neurologic illnesses of unknown etiology in the pediatric population. The pathophysiology of EBV neurologic complications has not been clearly delineated. The various neurologic symptoms have been attributed to direct viral invasion, immune complexes, and inflammatory reactions. Although infection and symptoms may coincide, a direct cause-and-effect relationship has yet to be determined. We reviewed the literature in order to present the wide variety of EBV-associated neurologic presentations.

Guillain-Barré Syndrome (GBS)

GBS has the most well-known association with EBV. It is typically an ascending paralysis of the extremities with albuminocytologic dissociation of the cerebrospinal fluid (CSF). Unusual variants occur, including the Miller Fisher syndrome (i.e., ophthalmoplegia, ataxia, areflexia) and multiple cranial neuropathies. GBS may be associated with EBV infections without clinically apparent IM [4,13,14].

In GBS, lymphocytes and macrophages have caused inflammation in the peripheral nervous system. It has been postulated that antimyelin antibody attachment to myelin antigen may precede macrophage stripping of the myelin lamellae [15].

Encephalitis/Meningitis

Encephalitis/meningitis was the first described neurologic complication of IM and is believed to be the most common. It may resemble an aseptic meningitis or encephalitis. EBV is the cause in up to 5% of all patients with acute viral encephalitis [16]. Several case reports described patients who presented primarily with signs and symptoms of meningitis and secondarily developed the stigmata of IM [17]. The symptoms may be acute in onset and rapidly progressive. It is usually associated with complete recovery, but fatal cases secondary to brain edema and herniation have been reported. Chorea occurred as a complication with EBV meningoencephalitis in several patients [18].

Changes in the spinal fluid are variable. The opening pressure is normal or slightly elevated. There is predominantly a mononuclear pleocytosis with most cell counts well below 22/mm^3. Reports included an atypical lymphocytosis in the CSF. Glucose and chloride determinations are normal. Protein level is normal to mildly elevated. Low titers of EBV capsid antigen have been measured in the CSF [10,19]. The meningitic symptoms are believed to be caused by lymphoid infiltration of the meninges. In 1970, Sworn and Urich presented the pathologic findings of an 8-year-old boy with IM who developed encephalitis 2 weeks into the illness and died [20]. Results of a brain biopsy, and later postmortem examination revealed patchy inflammatory lesions with dense perivascular cuffing and diffuse infiltration of the parenchyma with mononuclear cells, many of which were atypical. It is unknown whether this inflammatory response was due to direct viral invasion or immune complexes.

"Alice in Wonderland" syndrome (i.e., metamorphopsia) is an encephalopathy that presents as perceptual defects concerning size, shape, color, and spatial relationships of objects. It was first described by Todd in 1955 [21] and is a well-known occurrence in IM [5,22]. Metamorphopsia is related to lesions of the occipital, occipitotemporal, and occipitoparietal regions. Electroencephalographic (EEG) abnormalities in the parieto-occipital region have been reported in children with this illness [23].

Nonfebrile seizures have been reported as the major presenting sign of IM [6,11,24], in the majority of patients being part of the meningitic/encephalitic process. The seizure can be focal or generalized [25]. The EEG usually demonstrates increased slow wave activity, appearing either in paroxysms or in a continuous pattern. These generalized high-voltage slow waves often appear in multiple foci which can shift daily without accompanying neurologic phenomenon [26]. Residual neurologic deficits occur in 12% of patients [6,27].

Acute hemiplegia has been associated with EBV infection in older children (age range: 9-18 years) [28]. Most cases of acute hemiplegia of childhood occur within the first 3 years of life and have a number of known viral etiologies.

Two areas of controversy involve the association of EBV with multiple sclerosis (MS) and subacute sclerosing panencephalitis (SSPE). MS is an autoimmune, cell-mediated, inflammatory process resulting in focal areas of destruction of CNS myelinated fibers. Although the etiology remains unknown, evidence suggests that early-life viral infections may play a role in pathogenesis. Bray et al. reported that patients with MS had significantly higher seropositivity rates for EBV and higher serum viral capsid antigen IgG antibody than did controls [29]. Bray et al. subsequently described an association between neurologically complicated primary EBV infection and both chronic and acute central demyelinating disease in 5 patients [30]. Although they do not conclude that EBV causes MS, Bray et al. believed that it may play a role with other environmental and genetic factors.

SSPE is typically associated with prior measles infection, and is manifested by progressive intellectual deterioration, ataxia, myoclonus, seizures, and eventually

death. Scully and McNeely reviewed the case of a 13-year-old girl who presented with altered behavior and mood [31]. She had IM encephalitis without other classic IM symptoms. She developed SSPE resulting in death 10 weeks after initial presentation.

In 1975, Feorino et al. reported 3 children with SSPE whose conditions coincided with primary EBV infection. They concluded that EBV triggered a latent measles infection by interfering with the normal immunologic mechanism, rather than EBV being the primary cause of SSPE [32].

Hochberg et al. reported a 13-year-old girl who died of SSPE which occurred as part of an acute IM encephalitic illness [33]. Indirect florescent antibody staining of cerebral cortex sections revealed both measles and EBV antigenic material. Their findings supported those of Feorino et al. that defects in cellular immunity associated with IM may be responsible for activation of latent measles-like virus.

Cranial Nerve Palsy

In IM-related cranial neuropathies, most cranial nerves have been reported to be affected, either alone or in combination [34]. The majority of patients have been adolescents and young adults. Onset usually occurs after the diagnosis of IM, but may be an initial sign or begin as long as 2 months later. Prognosis is good and most patients recover within 4 months; the exception is sensorineural hearing loss which was reported to be a rapid, progressive, and permanent hearing loss occurring 1-4 months after an EBV infection [35].

The cranial nerve most often affected is the facial nerve, either isolated or bilaterally [36], and the association of Bell palsy with IM has been widely reported [37]. Most EBV cranial nerve palsies are associated with GBS and are rare in the absence of more diffuse neurologic involvement [38].

Optic Neuritis

A variety of optic nerve complications associated with IM has been reported and includes blurred vision, papilledema, optic neuritis, papilloretinal edema, and retrobulbar neuritis. Tanner divided the manifestations into two groups [39]: the first was due to direct involvement of the eye and adnexa and included conjunctivitis, eyelid/periorbital edema, uveitis, optic neuritis, papilledema, and retinal edema; and the second was due to CNS lesions affecting vision, and included extraocular muscle palsy, ptosis, nystagmus, scotoma, hippus, and disturbances of conjugate deviation.

Peripheral Neuropathy

Brachial plexus neuropathies have been widely reported, with patients as young as 18 months of age [40]. Watson and Ashby reported a 19-year-old boy who developed weak, painful shoulders 18 days after IM [41]. He had bilateral weakness and atrophy of the shoulder girdle and decreased sensation bilaterally in the axillary nerve distribution. His deficit cleared after 4 months. The postulated pathologic infectious mechanism was lymphatic drainage from the cervical lymph nodes to the region of the brachial plexus, involving the nerves by direct viral invasion or an immunologic response.

Although autonomic dysfunction can occur in GBS, several patients with isolated autonomic neuropathy associated with IM have been reported [42,43]. It is manifested as orthostatic hypotension, nausea, vomiting, anhidrosis, loss of lacrimation and salivation, pupillary abnormalities, and poor bowel or bladder function.

Cerebellar Ataxia

Acute cerebellar ataxia can present as the sole manifestation of IM, but the majority of patients have other systemic signs. Erzurum et al. reviewed the English literature in 1983 and reported 16 patients [12], all but one of whom were 4-26 years of age. Males were predominantly affected. The CSF findings were nondiagnostic, revealing mild mononuclear pleocytosis. Although the precise pathophysiology has not been ascertained, Wadhwa and Ghose speculated that cerebellar dysfunction resulted from virus-induced inflammatory changes within the CNS because antibodies to EBV capsid antigens were found in the CSF of patients with cerebellar ataxia [44]. The prognosis is excellent with complete recovery expected in all patients within 4 months.

Transverse Myelitis

In 1966, Cotton and Webb-Peploe reported a patient with transverse myelitis with laboratory findings confirming "glandular fever," but without pharyngitis, lymphadenopathy, or splenomegaly [45]. Transverse myelitis is the least common neurologic complication, but occurs more frequently in younger individuals than adults. Junker et al. recently reported a 14-year-old boy with acute-onset T11 transverse myelitis, with progressive paralysis of both legs over 36 hours [46]. Three weeks later, he developed the stigmata of IM with a positive heterophil test.

Conclusions

We emphasize the importance of recognizing EBV as a cause of acute neurologic illness in children and young adults. EBV infections have been associated with a multitude of disease processes with or without the stigmata of IM. Virus-specific serodiagnostic testing may be required to diagnose an atypical EBV infection. The pathogenesis of EBV-associated neurologic disorders remains speculative.

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